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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,990	07/09/2003	Henrik S. Olsen	PF108P2D1	8196

22195 7590 08/17/2004

HUMAN GENOME SCIENCES INC
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE, MD 20850

EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,990	OLSEN ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,16-32,48,63,78,103,121 and 139* is/are pending in the application.

4a) Of the above claim(s) *1,32,48,63,78,103 and 121* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-31 and 139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,16-32,48,63,78,103,121 and 139* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 16-31 and 139) in the reply filed on 23 June 2004 is acknowledged. The traversal is on the ground(s) that the Groups present do not present a serious search burden as they all pertain to stanniocalcin. This is not found persuasive because search and consideration of stanniocalcin is only part of the search for each Group. As detailed in the Restriction Requirement (23 April 2004) each Group is drawn to a separate and distinct invention. Each with its own non-overlapping search. Sharing stanniocalcin in common is insufficient to establish them as non-distinct inventions. The requirement is still deemed proper and is therefore made FINAL. Claims **1, 32, 48, 63, 78, 103,** and **121** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 June 2004.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

3. The disclosure is objected to because of the following informalities: paragraph **[0114]** has text blacked out; paragraph **[0115]** is missing; missing space "WO90/11092" **[0307]**; missing space "WO92/01047" **[0536], [0539]**. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims **16-31** and **139** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of increasing resistance of a cell to hypoxic stress, comprising contacting the cell with a stanniocalcin polypeptide comprising the amino acid sequence of SEQ ID NO: 2*, does not reasonably provide enablement for *fragments, sequence variants, muteins of SEQ ID NO: 2*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

5. The claims are drawn very broadly to a method of increasing resistance of a cell to hypoxic stress comprising contacting said cell with a fragment, a sequence variant, and/or a mutein of a stanniocalcin polypeptide comprising the amino acid sequence of SEQ ID NO: 2. The language of said claims encompasses both *in vivo* and *in vitro* uses and a wide range of stanniocalcin fragments.

6. The specification teaches that stanniocalcin (STC) is a hormone that regulates calcium and phosphate uptake in vertebrates including fish and humans. Paju (human neural cell line) transfected with the stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence increase the cells survival of when exposed to hypoxic insult *in vitro*. In addition, stanniocalcin is elevated in humans (patients) and rats (animal models) in ischemia.

7. However, the specification fails to provide any guidance for the successful use of fragments, sequence variants, and/or muteins of the stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence. Since resolution of the various complications in regards to targeting the effects fragments, sequence variants, and/or muteins of the stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations fragments, sequence variants, and/or muteins of the stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence to correlate with increased resistance to hypoxia. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of using fragments, sequence variants, and/or muteins of the stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence *in vivo* based solely on its performance *in vitro* of full-length stanniocalcin protein of the SEQ ID NO: 2 amino acid sequence is highly problematic (see

MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapies, such a disclosure would not be considered enabling since the state of protein biochemistry and endocrinology is highly unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of stanniocalcin.

10. On the breadth of the claims, Verbost & Fenwick (May 1995) "N-terminal and C-terminal fragments of the hormone stanniocalcin show differential effects in eels." Gen Comp Endocrinol. **98**(2): 185-92 that stanniocalcin (STC) is the primary hypocalcemic hormone in fish. Verbost & Fenwick tested the effects of an N-terminal [peptide U ($eSTC_{1-20}$)], a C-terminal [peptide V ($eSTC_{103-136}$)], and a mid-fragment [peptide W ($eSTC_{202-231}$)] of stanniocalcin on plasma total and free (ionic) calcium levels and whole animal calcium influx in eels (Figure 1). Both the N- and the C-terminal fragments were hypocalcemic, causing 18 and 12% reduction in plasma calcium in stanniectomized eels, respectively. The N-terminal fragment caused more hypocalcemia than the C-terminal fragment. The mid-fragment had no effect on plasma calcium or calcium influx. Thus different STC fragments have different effects (Table 1). In addition, the

STC fragments vary in their activity dependent upon the species in which it was tested due to differences in sequence among different STCs (pp. 190-191). Thus the skilled artisan is confronted by unpredictability of the bioactivity of STC fragments.

11. On the nature of the invention, Yoshiko *et al.* (28 May 1996) "Effects of a synthetic N-terminal fragment of stanniocalcin on the metabolism of mammalian bone in vitro." Biochim Biophys Acta. **1311**(3): 143-9 teaches that an N-terminal amino acid residues of stanniocalcin (STC_{1-20}) inhibited increases in the number of tartrate-resistant acid phosphatase-positive, multinucleated cells promoted by an N-terminal fragment of human parathyroid hormone ($hPTH_{1-34}$) in cultures of murine hemopoietic cells (Figures 1-2). STC_{1-20} also slightly decreased the rate of loss of radioactivity from calvariae of fetal rats that had been prelabeled with ^{45}Ca, both with and without stimulation by $hPTH_{1-34}$ (Figures 3-4). The accumulation of cAMP induced by $hPTH_{1-34}$ in ROS 17/2.8-5 cells was suppressed by STC_{1-20}. Treatment with STC_{1-20} caused increases of the rate of incorporation of [^{3}H]proline into the collagenase-digestible protein of calvariae in newborn mice (Table 1). Therefore a STC fragment, STC_{1-20}, has diverse effects on the metabolism of mammalian bone, causing a biphasic response. Therefore the skilled artisan is confronted with an undue burden of experimentation to first determine structure of the STC fragments to be used in the claims, their activity, and then their suitability for use to fulfill the preamble of the claims.

12. On the state of the prior art, Stern *et al.* (November 1991) "Salmon stanniocalcin and bovine parathyroid hormone have dissimilar actions on mammalian bone." J Bone Miner Res. **6**(11): 1153-9 (**IDS#N**) teaches that salmon STC failed to effect the serum calcium levels of parathyroidectomized rats at concentrations equimolar with effective concentrations of

parathyroid hormone (PTH) (Table 1). STC did not increase cAMP in ROS 17/2.8 or UMR-108 osteosarcoma cells, OK kidney cells, fetal rat limb bones, or neonatal mouse calvariae, and similarly failed to increase urinary cAMP in rats (Table 2; Figure 1). Therefore salmon STC does not have the same effects in mammals as it does in fish. Thus the skilled artisan is left to experiment with an unpredictable protein to determine if it has the desired effects of protecting from hypoxic stress in mammals.

13. Regarding derivatives and fragments of the SEQ ID NO: 2 polypeptide, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g.

such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex

nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Therefore due to the large quantity of experimentation necessary to identify all the applicable fragments of SEQ ID NO: 2, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable fragments of SEQ ID NO: 2, the absence of working examples directed to known fragments of SEQ ID NO: 2, the complex nature of the invention, the unpredictability of the effects of fragments of SEQ ID NO: 2 on cells and/or patients (see references above) and the breadth of the claims which fail to recite limitations for what constitutes an applicable fragments of SEQ ID NO: 2, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Claims **16-31** and **139** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. The claims are drawn to polypeptides having at least 90% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological

activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

17. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 2. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

18. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of

the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

19. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

20. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

21. Claim **16** is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel polypeptide (i.e., SEQ ID NO: 2). Since the cDNA of claim 16(d) is essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public.

22. If the cDNA is not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the cDNA. The specification does not disclose a repeatable process to obtain the cDNA and it is not apparent if the cDNA is readily available to the public. It is

noted that Applicant has deposited the cDNA (ATCC Deposit Number 75652) (pp. 7 of the specification), but there is no indication in the specification as to public availability.

23. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the cDNA will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

> (a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
> (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
> (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
> (d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and
> (e) the deposit will be replaced if it should ever become inviable.

24. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to

permit examination." Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Summary

25. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
August 9, 2004

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